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This research is aimed at developing a new optical approach, called "Photon Migration Imaging", for breast cancer detection and diagnosis. The project will develop computer software and conduct phantom experiments to achieve the proposed goals. At the conclusion of this project, we are pleased to report that we have completed the proposed goals. In this final report, we summarize our accomplishments in the proposed research areas.

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Introduction

The ability of near-infrared (NIR) light-based techniques to noninvasively image and analyze tissue structure and function promises their great potential for detection and diagnosis of breast cancer. Optical diagnostic techniques allow us to not only enhance the existing capabilities, but to eliminate the need for physical biopsies. In addition, optical imaging is inexpensive and portable, which indicates that optical imaging could be an ideal candidate for routine breast screening. However, since the scattering properties of tissues convolute re-emitted NIR signals, the extraction of pertinent information continues to remain elusive. An understanding of light propagation and light-tissue interaction is required before the optical technologies can substantially impact diagnostic medicine.

Research efforts in the Biomedical Optics Laboratory at Clemson University are focused on the biophysics of light propagation and light-tissue interaction in order to engineer appropriate approaches for noninvasive breast imaging and spectroscopy. Specifically, we are developing indirect optical/fluorescence approaches using photon migration measurements in the continuous-wave and frequency domains. These indirect optical/fluorescence approaches or image reconstructions are computationally based on the powerful finite element methods. A CCD-based optical spectroscopic imaging system is already operational in our laboratory for continuous-wave tomographic photon migration measurements, while a frequency-domain system has also been constructed. Using these optical systems coupled with our finite element based reconstruction algorithms, we will be able to extract spatial/spectroscopic maps of tissue optical properties, lifetime and/or yield of endogenous and exogenous fluorescent probes. Since metabolic tissue states can be identified by our approaches, diagnostic information is also obtained in addition to detection of tumor.

This Career Development application for support of Dr. Huabei Jiang will facilitate the establishment/continuation of these research activities. Interdisciplinary interactions with the Greenville Hospital System (Greenville, SC) will be enhanced, which insures the direction of research towards a clinically pertinent and feasible system.

Body

This report describes work accomplished during the entire five years of a proposed four-year study (with one-year no-cost extension). This Career Award supports Dr. Jiang's research on optical and fluorescence imaging using both continuous-wave and frequency-domain measurements. Here we summarize our work in all the proposed areas including the implementation of image reconstruction software and evaluation of the reconstruction software using extensive phantom experiments.

Software work

While we have implemented some of the proposed image enhancing schemes in the current 2D codes including the total variation minimization, weighted least squares criterion and low pass filtering, we have also developed two additional novel schemes that were not proposed originally. Our existing algorithms require an additional calibration measurement with a homogeneous phantom in order to determine the

excitation source strength and the boundary conditions coefficient that are critical for a successful reconstruction. The first scheme, which uses the idea of normalizing the photon density in the reconstruction algorithm, allows for the reconstruction of optical property images without measuring the excitation source strength. The second scheme, which is based on a simple least-squares minimization between the measured and computed photon densities at the boundary, can provide us the boundary conditions coefficient. The normalizing scheme-based algorithm eliminates the need of absolute measurement data for reconstruction, yet provides us absolute quantitative optical images. We have tested these two schemes using simulations in which noise-free and noisy "measured" data are applied. We have also confirmed these simulations using tissue-like phantom experiments.

We have continually evaluated and optimized the important image enhancing schemes described above. We have implemented and evaluated important image enhancing schemes in the areas of boundary conditions and source/detector models. We have also derived a photon diffusion equation that considers the impact of tissue refractive index. Extensive simulation and phantom experiments have been conducted to complete these software developments. We have implemented the 3D reconstruction algorithms.

We have implemented and evaluated important image enhancing schemes in the areas of dual meshing and total variation. Extensive simulation and phantom experiments have been conducted to complete these software developments. We have also implemented the 3D reconstruction algorithms based on these image enhancing schemes.

Phantom Experiments

Using our frequency-domain imaging system, we have conducted extensive phantom experiments for both optical and fluorescence reconstruction with dye-free background and dye-laden background. Our experimental setup used was the automated multi-channel frequency-domain system mentioned above. The system employed a radio-frequency intensity-modulated near-infrared beam. The laser beam was sent to the phantom by 16 fiber optic bundles coupled with a high precision moving stage. The diffused radiation was received by another 16 channel fiber optic bundles and delivered to a thermo-electric cooled PMT. A second PMT was used to record the reference signal. These PMTs were supplied at a radio-frequency modulated current with 0.1-1KHz shift. The intermediary frequency signal obtained from the PMTs was processed using a National Instruments board. For every source position, 16 measurements for each detector were made, taking alternatively 100 ms samples for sample and reference signals. Fluorescence signals were obtained through an 830nm or 690nm interference filter placed in front of the detection PMT. dc, ac intensity and phase shift between reference and sample signals were obtained using FFT Labview routines. The total data collection time for 256 measurements was 8 minutes.

We have shown that we are able to obtain simultaneous reconstruction of both lifetime and yield images in turbid media using ac excitation and fluorescent data. While an ideal, perfect uptake of fluorescent dye in the target has been assumed, this study

has clearly demonstrated the feasibility of fluorescence lifetime imaging in turbid media using the reconstruction approach described here.

Solid phantom was used to mimic the human tissue. It was made of agar, Intralipid, black ink and fluorescent dyes. The absorption and the reduced scattering coefficients are linear with the ink and Intralipid concentrations, respectively. Micromolar ICG and DTTCI dyes were added in the tissue phantom to provide the fluorescence contrast. Agar is used to make the phantom solid. The solid phantom consisted of a cylindrical background and a cylindrical heterogeneity. The absorption peaks of ICG and DTTCI are 764 nm and 780 nm, respectively. And the fluorescent emission peaks of them are 803 nm and 830 nm respectively. Their lifetimes in water were measured to be 0.56 ns and 1.18 ns, respectively. A laser diode of wavelength 785 nm was used to excite both dyes, and the emission light of wavelength at 830 nm were detected for both of them through an interference filter of center wavelength 830 nm with 10nm bandwidth. Successful images have been reconstructed.

While ICG and DTTCI dyes were continually used in these experiments, we have also used oxygen-sensitive dyes including Pd chlorin e6 and Pd meso-tetra (4-carboxyphenyl) chlorin and Sn(IV)Chlorin-e_6-Cl_2-3Na (SCCN). Agar was used to make the phantom solid. The absorption and fluorescent emission peaks of these two dyes are about 635 nm and 660nm, respectively. The solid phantom consisted of a cylindrical background and a cylindrical heterogeneity. These experiments show that we may be able to obtain the tissue oxygen concentration images by the use of oxygen-sensitive dyes. This could provide optical imaging a unique capability to distinguish between benign and malignant breast tumors because the oxygen concentration in these two types of tumors often is distinct.

Key Research Accomplishments

1. We have developed a number of novel schemes that can enhance our current 2D reconstruction software.
2. We have constructed and tested a muti-channel frequency-domain imaging system. We have conducted phantom experiments that confirmed our software enhancement.
3. We have improved the multi-channel frequency-domain imaging system.
4. We have conducted extensive phantom experiments for fluorescence lifetime imaging. The successful experiments have confirmed the imaging capability of our reconstruction software.
5. We have implemented and evaluated the 2D image enhancing schemes especially in the areas of dual meshing and total variation. We have also started to implement the 3D reconstruction algorithms based on these image enhancing schemes. We have conducted considerable phantom experiments for evaluating these image enhancing schemes and 3D algorithms.

Reportable Outcomes (Copies of these papers have been provided as Appendices to the previous Annual Reports)

1. N. Iftimia, H. Jiang, "Quantitative optical image reconstruction of turbid media by using direct-current measurements", *Appl. Opt.* **39**, 5256-5261(2000).

2. Huabei Jiang, Sathappan Ramesh, Matthew Bartlett, "Combined optical and fluorescence imaging for breast cancer detection and diagnosis", *Critical Rev. in Biomed. Engr.* **28**, 371-375(2000).

3. N. Iftimia, S. Liao, H. Jiang, "Development of a combined optical and fluorescence imaging system in frequency-domain for breast cancer detection", *Proc. OSA Biomedical Meetings*, 383-385(2000).

4. Ye Yang, Nicusor Iftimia, Yong Xu, Huabei Jiang, "Frequency-domain fluorescent diffusion tomography of turbid media and *in vivo* tissues", *Proc. of SPIE* **4250**, 537-545(2001).

5. Q. Lu, Y. Xu, H. Jiang, "The diffusion approximation model for turbid media with a spatially varying refractive index: impact of skin on optical breast imaging", *Proc. OSA Biomedical Topical Meetings: Advances in Optical Imaging and Photon Migration*, 93-95(2002).

6. E. Shives, Y. Xu, N. Iftimia, H. Jiang, "Fluorescent lifetime tomography using frequency-domain data", *Proc. OSA Biomedical Topical Meetings: Advances in Optical Imaging and Photon Migration*, 519-520(2002).

7. E. Shives, Y. Xu, and H. Jiang, "Fluorescence lifetime tomography of turbid media based on an oxygen-sensitive dye," *Opt. Express* **10**, 1557-1562 (2002).

Conclusions

We have made a significant progress that has fulfilled the statement of work proposed for this project. The results generated from this project will allow the PI to submit several proposals to agencies such as NIH for continuing research in the area supported by this Career Development Award.